AMENDMENTS TO THE CLAIMS

Please amend the claims as set forth below. The complete set of claims is provided below in compliance with the Revised 37 C.F.R. § 1.121, Effective July 30, 2003. The status of each claim is shown next to each claim number; current additions are shown by underlines and deletions are shown by strikethrough.

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1. (Currently Amended) A set of promoter sequences derived from Gram-positive bacteria, Gram-negative bacteria or fungi, said set of promoter sequences being suitable for optimizing the expression of a gene in a selected microorganism ~~or group of organisms~~, said set of promoter sequences covering a range of promoter activities for said gene in said selected microorganism in small steps each step changing the activity by 50-100%, each promoter sequence of said set of promoter sequences comprising a double stranded DNA sequence, the sense strands of which comprise

> at least two consensus sequences, said at least two consensus sequences corresponding to conserved sequences identified in said selected microorganism, at least half of each of said consensus sequences being kept constant in the set of promoter sequences, the at least two consensus sequences, when the selected microorganism ~~or group of organisms~~ is
>
> > a) a prokaryotic microorganism, said at least two consensus sequences being selected from the group consisting of TATAAT, TTGACA and an activator binding site upstream of the TATAAT sequence, or

b) ~~when the selected organism of group of organisms~~ is an eukaryotic microorganism, said at least two consensus sequences being selected from the group consisting of a TATA-box and a UAS upstream of said TATA-box and,

between said consensus sequences or flanking at least one of said consensus sequences, at least one nucleotide spacer sequence, at least part of which, relative to the corresponding spacer sequence of the identified promoter, is varied by random incorporation of nucleotides that are selected Rom the group consisting of the nucleobases A, T, C and G.

2. (Previously Presented) A set of promoter sequences according to claim 1 wherein at least 10 nucleotides in the at least one nucleotide spacer sequence are selected randomly from the group consisting of the nucleobases A, T, C and G.

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3. (Previously Presented) A set of promoter sequences according to claim 1 wherein each of the promoter sequences comprises a regulatory DNA sequence imparting a specific regulatory feature to each of the promoter sequences.

4. (Previously Presented) A set of promoter sequences according to claim 1 wherein each of the promoter sequences members comprises at least one recognition site for a restriction endonuclease.

5. (Cancelled)

6. (Currently Amended) A set of promoter sequences according to claim [[5]] 1 wherein the selected microorganism is selected from the group consisting of prokaryotic microorganisms where the consensus sequences comprise at least 3 conserved nucleotides of the -10 signal TATAAT.

7. (Previously Presented) A set of promoter sequences according to claim 5 wherein the consensus sequences comprise at least 3 conserved nucleotides of the -35 signal TTGACA.

8. (Previously Presented) A set of promoter sequences according to claim 5 wherein each of the promoter sequences comprise at least one conserved motif selected from the group consisting of AGTT at positions -44 to -41, TATTC at positions -40 to -35, TG at position -15 to -14 and GTACTGTT at positions +1 to +8.

9. (Previously Presented) A set of promoter sequences according to claim 5 comprising at least two promoter sequences selected from the group consisting of SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37,SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42.

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10. (Previously Presented) A set of promoter sequences according to claim 7 wherein the spacer sequence between the -35 and the -10 signal is 14-23 bp.

11. (Previously Presented) A set of promoter sequences according to claim 5 wherein the promoter sequences comprise a sequence selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO:2.

12. (Cancelled)

13. (Currently Amended) A set of promoter sequences according to claim [[12]] 1 wherein the selected microorganism is selected from the group consisting

of eukaryotic microorganisms where the consensus sequences comprise a TATA box and at least one upstream activation sequence (UAS).

14. (Previously Presented) A set of promoter sequences according to claim 12 wherein the promoter sequence is SEQ ID NO:3.

15. (Currently Amended) An isolated set of promoter sequences according to claim 12 comprising at least two promoter sequences selected from the group consisting of SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, and SEQ ID NO:58.

16. (Currently Amended) A method of constructing a set of promoter sequences which is suitable for optimizing the expression of a gene in a selected microorganism, said set of promoter sequences covering a range of promoter activities for said gene, the method comprising: ~~the steps of~~

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(i) identifying in said microorganism a promoter sequence comprising at least two consensus sequences, which consensus sequences correspond to conserved sequences identified in said microorganism, at least one of the consensus sequences being flanked by a non-conserved nucleotide spacer sequence or both ~~or~~ of said consensus sequences being separated by the non-conserved nucleotide spacer sequence, the at least two consensus sequences, when the selected microorganism is

(a) a prokaryotic microorganism, said at least two consensus sequences being selected from the group consisting of TATAAT, TTGACA and an activator binding site upstream of the TATAAT sequence, or

(b) ~~when the selected organism or group of organisms is~~ an eukayotic microorganism, said at least two consensus sequences

being selected from the group consisting of a TATA-box and a UAS upstream of said TATA-box,

(ii) constructing a set of single stranded DNA sequences each of which comprises at least half of each of the consensus sequences, and a non-conserved nucleotide spacer sequence, at least part of which is varied by a random incorporation of nucleotides selected from the group consisting of the nucleobases A, T, C and G, whilst keeping the at least half of the consensus sequences constant, and

(iii) converting the single stranded DNA sequences into double stranded DNA sequences to obtain the set of promoter sequences covering a range of promoter activities for said gene.

17. (Currently Amended) A method according to claim 16 wherein ~~the set of promoter sequences obtained spans, with respect to promoter activities for said gene, the range in steps, each step changing the activity by 50-100%~~ a plurality of promoter sequences is selected from the set of promoter sequences, said plurality of promoter sequences covering a range of promoter activities for said gene, in steps, each step changing the promoter activity by 50-100%.

18. (Currently Amended) A method of controlling in ~~an~~ microorganism the flux of a cellular metabolite or the expression of a desired gene product, said method comprising at least one step of changing the expression level of at least one gene in the pathway leading to formation of said metabolite or the expression level of said desired gene product~~, the step~~ comprising

(i)selecting from ~~the~~ a set of promoter sequences ~~of~~ suitable for optimizing the expression of a gene in a selected microorganism, said set of promoter sequences covering a range of promoter activities for said gene is said selected microorganism in

small steps each step changing the activity by 50-100%, each promoter sequence of said set of promoter sequences comprising a double stranded DNA sequence, the sense strands of which comprise

at least two consensus sequences, said at least two consensus sequences corresponding to conserved sequences identified in said microorganism, at least half of each of said consensus sequences being kept constant in the set of promoter sequences,the at least two consensus sequences, when the selected microorganism is

a) a prokaryotic microorganism, said at least two consensus sequences being selected from the group consisting of TATAAT, TTGACA and an activator binding site upstream of the TATAAT sequence, or

b) an eukaryotic microorginism, said at least two consensus sequences being selected from the group consisting of a TATA-box and a UAS upstream of said TATA-box and,

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between said consensus sequences or flanking at least one of said consensus sequences, at least one nucleotide spacer sequence, at least part of which, relative to the corresponding spacer sequence of the identified promoter, is varied by random incorporation of nucleotides that are selected from the group consisting of the nulcleobases A, T, C and G, ~~claim 1 a plurality of promoter sequences covering a range of promoter activities for said gene, in steps, each step changing the promoter activity by 50-100%,~~

(ii) transforming said set of promoter sequences into cells of the organism, placing in each of said cells the gene to be expressed under the control of at least one promoter of the set,

(iii) cultivating the transformed cells to obtain clones thereof and selecting among said clones a clone having, relative to an otherwise identical clone where the at least one gene in the pathway or the gene expressing the desired gene product is under the control of its native promoter, a higher or a lower flux of the cellular metabolite or a higher or a lower expression of the desired gene product.

19. (Cancelled)

20. (Cancelled)

21. (Currently Amended) A method of isolating a promoter sequence being capable of optimizing the expression of ~~a gene~~ at least one gene in the pathway or a gene expressing a desired gene product in a selected microorganism, the method comprising

(i) constructing, using the method of claim 16, a set of promoters covering a range of promoter activities for said gene, in steps, each step changing the ~~B-galactosidase~~ promoter activity by 50-100%,

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(ii) transforming said set of promoters into cells of the selected microorganism, placing in each of said cells the gene to be expressed under the control of at least one promoter of the set,

(iii) cultivating the transformed cells to obtain clones thereof and selecting among said clones a clone having, relative to an otherwise identical clone where the at least one gene in the pathway or the gene expressing the desired gene product is under the control of its native promoter, a higher or a lower flux of the cellular metabolite or a higher or a lower expression of the desired gene product, and

(iv) isolating said promoter sequence from the clone.

22. (Currently Amended) ~~A~~ An isolated promoter sequence selected from the group consisting of SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, and SEQ ID NO:58.

23. (Currently Amended) A set of promoters according to claim 1 suitable for optimizing the expression of a gene in a prokaryotic microorganism wherein the promoter sequences comprise a sequence selected from the group consisting of AGTT, TATTC, TG, TTGA, TTGG, and GTACTGTT.

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24. (Cancelled)

25. (Currently Amended) A set of promoters according to claim 1 where, when the selected microorganism ~~or group of organisms~~ is eukaryotic, the TATA-box is the TATAAA sequence.

26. (Cancelled)

27. (Currently Amended) A set of promoters according to claim 1 where, when the selected microorganism ~~or group of organisms~~ is eukaryotic, the UAS is UAS_{GCN4p}.